CLINICAL MICROBIOLOGY REVIEWS, Jan. 2010, p. 14–34 Vol. 23, No. 1
0893-8512/10/$12.00 doi:10.1128/CMR.00034-09

Rifampin Combination Therapy for Nonmycobacterial Infections

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INTRODUCTION

Rifampin was approved by the Food and Drug Administration (FDA) in 1971 for the treatment of patients with tuberculosis and asymptomatic carriers of *Neisseria meningitides*, and 4 decades later, these are still the only approved indications (220). Because of its low toxicity, rifampin use has expanded greatly as a combination antimicrobial therapy for the treatment of various infections, from the common *Staphylococcus aureus* to uncommon fungal organisms (212).

The topic of rifampin combination therapy for the treatment of nonmycobacterial infections is very controversial, with much of the use based on clinical experience rather than proven evidence. With the current emergence of multidrug-resistant (MDR) bacteria, especially methicillin-resistant *S. aureus* (MRSA) in all clinical settings (145), there are increasing case studies reporting the use of rifampin combination therapies for treatment. This review will evaluate the laboratory and clinical data associated with the use of rifampin combination therapies for nonmycobacterial infections and the pharmacological interactions of rifampin. The largest component of this review will focus on staphylococcal infections but

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will include other bacteria for which its use has recently expanded. This review will not discuss rifampin use for skin decolonization, leprosy, brucellosis, or noninfectious disease.

BACKGROUND

Rifampin is a semisynthetic antibiotic derivative of rifamycin SV, which was first isolated from *Streptomyces mediterranei* in 1957. Rifampin acts by inhibiting DNA-dependent RNA polymerase, making it bactericidal (201). The development of rifampin was significant in overcoming drug-resistant tuberculosis in the 1960s, as it killed rapidly dividing bacilli as well as the long-lived persistent forms. As with other therapies for tuberculosis, it was soon recognized that rifampin monotherapy quickly resulted in rifampin resistance.

Rifampin was also initially studied as an antiviral (in particular the poxviruses, based on the viruses containing an RNA polymerase) and as an antifungal agent combined with amphotericin B in the early 1970s (27, 116, 175, 212, 235). The antiviral activity of rifampin did not progress from laboratory studies because the required rifampin dosage needed to achieve treatment levels would be toxic, while more effective antifungal agents with less toxicity were later developed that made the role of rifampin antifungal synergy redundant (27, 116, 175, 212).

Staphylococcal infections were one of the first nonmycobacterial diseases treated with rifampin therapy; however, it was soon discovered that to prevent the emergence of rifampin-resistant isolates, at least another active antimicrobial agent was required to be used with rifampin (17). Jensen subsequently showed that although rifampin combination therapy was effective against severe staphylococcal infections, rifampin resistance still emerged (130). Importantly, that author observed that the combined therapy had better treatment responses for infections where there was a "lower organism burden"; in that example, it was urinary tract infections (130, 131).

The rifampin MICs against many bacterial organisms were determined in the late 1960s (13, 152, 165). Rifampin is active *in vitro* against *S. aureus*, *Staphylococcus albus* (*Staphylococcus epidermidis*), streptococcal organisms (including *Streptococcus pneumoniae*), *Clostridium welchii*, *Neisseria meningitidis*, and *Pasteurella multocida* (13, 152, 165). Rifampin has also demonstrated some *in vitro* activity against *Haemophilus influenzae* and *Bacteroides* sp. but was inconsistent for the treatment of *Pseudomonas aeruginosa*, *Klebsiella*, *Proteus*, *Salmonella*, and *Shigella* infections (13, 152, 165).

The observation of the "skip" tube phenomenon in rifampin combination therapy studies makes interpretations of minimal bactericidal concentration (MBC) results difficult. The "skip" phenomenon can be demonstrated when serial dilutions are performed to determine the MBCs of combination therapy. Initially, there is no growth of the bacteria in tubes at lower antibiotic concentrations, but growth then occurs in occasional tubes at higher antibiotic concentrations (201). This "skip" effect is due to the presence of rifampin-resistant mutants within the inocula and is found at a proportion of $1:10^6$ to $1:10^7$ within many strains of *S. aureus* (165, 201). Despite the excellent bactericidal activity of rifampin, it is the rapid emergence of resistance by the selection of these mutants that has limited its use. It is this propensity for emerging resistance upon therapy that has led to the use of rifampin in combination therapy for the treatment of many bacterial infections, with one of the first clinical reports of the use of rifampin combined with erythromycin for *S. aureus* endocarditis (194).

Rifampin Resistance

The causes of rifampin-resistant mutations within bacteria are due to alterations in the *rpoB* gene, which encodes the β-subunit of the RNA polymerase enzyme (41). There is no consistent pattern in which amino acids can be affected within the *rpoB* gene to cause resistance; however, codons 531 and 522 appear to be most frequently involved (41, 268). Rifampin resistance can develop through either insertions, deletions, or point mutations in the *rpoB* gene and depends on the bacterial organism affected (263, 268). The *rpoB* gene can be utilized to determine if there are clonal outbreaks of rifampin-resistant organisms in clinical settings (84).

There have been over 1,500 case reports and *in vitro* studies in the literature since the late 1960s on combination therapies of rifampin and other antibiotics; however, very few have been prospective human clinical studies (181, 220).

PHARMACOLOGY

Pharmacokinetics

Rifampin comes in both oral and intravenous formulations and has excellent oral bioavailability (30, 201). Rifampin is well absorbed from the gastrointestinal tract, especially on an empty stomach; reaches peak concentrations within 2 h in serum; and has a mean half-life of about 4 h for healthy patients, but it is increased for patients with renal and hepatic insufficiency (30, 197, 201). Rifampin is readily excreted in the bile and undergoes enterohepatic recirculation to maintain serum levels (201). It is 85% protein bound, with the unbound fraction being nonionized, allowing penetration into many tissues (7, 201). Rifampin does cross the placenta and also enters breast milk (201).

Rifampin enters the cerebrospinal fluid (CSF) adequately. A single 600-mg intravenous dose of rifampin for seven patients with uninflamed meninges produced peak CSF concentrations of 0.57 to 1.24 μg/ml and had slow CSF elimination (180). The overall penetration of rifampin into the CSF as a ratio of serum was 0.13 to 0.42 (median, 0.22), suggesting favorable pharmacokinetics for uninflamed meninges. Rifampin also has good penetration into the CSF when the meninges are inflamed. This was shown for children with meningitis receiving 20 mg/kg of body weight/day orally, who had concentrations of 1 μg/ml with a CSF-to-serum ratio of 0.21, which was similar to data for uninflamed meninges (146). Therefore, rifampin has excellent CSF activity for treating meningitis. However, its penetration into the brain is poor, as an animal model determined that rifampin penetrates the cerebral extracellular space with 0.3 to 1% of the serum concentration (168).

Side Effects

The most notable side effects of rifampin treatment are turning bodily fluids red and pill esophagitis (174, 201, 230). Although its side effect profile is relatively mild, serious reac-

TABLE 1. Nonantimicrobial drugs with major drug interactions or contraindications when used with rifampin[a]

Immunosuppressive drug	Endocrine drug	Cardiac drug	Neurologic drug	Other drug
Tacrolimus	Simvastatin	Diltiazem	Diazepam	Cimetidine
Sirolimus	Repaglinide	Digoxin	Barbiturates	Methadone
Corticosteroids	Clofibrate	Disopyramide	Buspirone	Opiates
Mycophenolate	Contraceptives	Lorcainide	Haloperidol	Ondansetron
Cyclosporine	Estrogen	Metoprolol	Midazolam	Sulfasalazine
	Glyburide	Mexiletine	Nitrazepam	Theophylline
	Tamoxifen	Nifedipine	Nortriptyline	Bendamustine
	Thyroxine	Propafenone	Phenytoin	Imatinib
	Rosiglitazone	Propranolol	Sertraline	
	Pioglitazone	Quinidine	Zolpidem	
	Ranolazine	Tocainide	Clozapine	
	Bosentan	Verapamil	Lamotrigine	
		Losartan		
		Warfarin		

[a] Data from references 14, 32, 46, 85, 122, 183, 214, and 274.

tions that have been reported include hepatotoxicity and nephrotoxicity (most commonly interstitial nephritis), while unexplained fevers, cytopenias, and neurological disturbances have also been reported (151, 220). The use of rifampin for patients with underlying hepatitis C virus (HCV) infection may increase the risk of hepatotoxicity (214).

Drug Interactions

Rifampin is a potent inducer of the cytochrome P450 (CYP) oxidative pathway, in particular the CYP3A4 enzymes in both the liver and intestinal wall as well as the P glycoprotein (PGP) transport system in the intestine (14, 274). This induction can result in significant interactions with many drugs including antimicrobial agents (14, 199). The list of drugs that rifampin can affect when either starting or discontinuing therapy is extensive, as summarized in Table 1. It is very important for clinicians ensure that drug interactions have been assessed before rifampin therapy is initiated, especially in association with immunosuppressive agents and warfarin. Rifampin has significant interactions with antifungal agents, especially the newer azoles (voriconazole) and human immunodeficiency virus (HIV) medications (efavirenz and protease inhibitors), as shown in Table 2. Also, there are important interactions with several frequently used antibiotics.

There have now been many combination therapy studies using rifampin and antibiotics, but the following section will focus on the more common, presently used antibiotics and will review its effect on synergy studies and antibiotic drug concentrations.

RIFAMPIN COMBINATION THERAPY

Staphylococci

There are numerous *in vitro* studies and case reports of rifampin combination antimicrobial therapy for the treatment of staphylococcal infections (13, 130, 165). This will be the largest focus of this review, and we will evaluate the combination of rifampin with other antibiotics for the treatment of *S. aureus* infections including for the management of methicillin-susceptible *S. aureus* (MSSA) infections, methicillin-resistant *S. aureus* (MRSA) infections, and infections with coagulase-negative staphylococci (CoNS). A summary of the *in vitro* studies and methodologies used (checkerboard, time-kill, and Etest methodologies) is shown in Table 3.

***In vitro* studies. (i) Definitions.** There are several *in vitro* methods that have been used to assess rifampin combination therapy. These include the checkerboard test, time-kill studies, serum bactericidal activity (SBA), disc diffusion, and Etest. Many of these studies are rarely performed in clinical laboratories now, as they can be time-consuming and labor-intensive, and their results (e.g., SBA) have rarely correlated with clinical outcomes (170, 199). Standard guidelines for the serum bactericidal test (SBT) were approved in 1999, and debates among investigators on the dilution required for bactericidal activity make interpretations of their results difficult (178, 202, 234, 265).

There were also inconsistent terminologies and methodologies reported by laboratories used to describe the effect of rifampin combination therapies on bacteria, making comparisons of the results problematic for this review. Rifampin combination therapy is commonly used to obtain "synergy" with other antibiotics, but standardizing the interpretations reported and the method used is essential for determining the overall effect on the tested bacteria.

"Synergy" is defined as the demonstration of either inhibitory or bactericidal activity that is greater than would be expected by merely the sum of the activities of the individual antibiotics (170).

"Additivity" or "indifference" is when the inhibitory activity of both of the agents is equal to the sum of the activity of the individual agents if they were used separately.

"Antagonism" is when the activity is significantly less than the additive effect of the two agents (144, 170).

The application of *in vitro* test results from combination therapies to clinical practice should be cautiously assessed (144). This is because *in vitro* testing does not include the drugs' hepatic and renal metabolisms, serum protein binding, drug distribution and half-life, as well as other drug interactions (170). Alterations in any one of the antibiotics' pharmacokinetic characteristics could result in rifampin monotherapy against the bacteria and the subsequent emergence of rifampin-resistant strains (220). The *in vitro* results from rifampin combina-

TABLE 2. Significant rifampin drug interactions with antimicrobial agents[a]

Antimicrobial	Interaction(s)	Recommendation	Description	Reference(s)
Antibiotics				
Atovaquone	↓ C_{ss} 54%	Contraindicated	Combination not recommended	6, 104
Clarithromycin	↓ CL 90%	No dosage adjustment	Despite reduced levels, still effective with *Mycobacterium avium* complex treatment	257
Dapsone	↓ C_{ss} 7- to 10-fold	No dosage adjustment	Effective combination for leprosy	125, 127, 275
Doxycycline	↓ C_{max} 60-70%	No dosage adjustment	Effective combination for *Brucella*	54
Linezolid	↓ C_{max} 41%, ↓ C_{min} 59%	No dosage adjustment	Gut P glycoprotein metabolism; concern for decreased levels clinically	76, 98
Moxifloxacin	↓ AUC 31%, ↓ C_{max} 32%	No dose adjustment recommended	Reduced glucuronidation; concern for levels of moxifloxacin	184
Metronidazole	↓ AUC 33%, ↑ CL 44%	No dose adjustment recommended		67
Antifungals				
Caspofungin	↓ C_{min} 31%	Raise caspofungin dose to 70 mg i.v. daily		233
Fluconazole	↓ AUC 22%, ↓ C_{max} 17%, ↑ CL 30%	Consider raising fluconazole dose	Would increase dose if used together	192
Itraconazole	Undetectable levels (case report)	Combination not recommended		71
Ketoconazole	↓ AUC, ↓ C_{max} (levels not available)	Combination not recommended		68
Voriconazole	↓ AUC 93%, ↓ C_{max} 96%	Contraindicated		99
Posaconazole	↓ AUC, ↓ C_{max} (levels not available)	Combination not recommended	Warning in package insert, no clinical data	221
HIV medications				
NRTI				
Zidovudine	↓ AUC 47%, ↓ C_{max} 43%	No dose adjustment recommended		97
NNRTI				
Delavirdine	↑ CL 27-fold, ↓ C_{max} 92%, undetectable C_{min}	Contraindicated	No longer manufactured	33
Efavirenz	↓ AUC 22%, ↓ C_{max} 24%, ↓ C_{min} 25%	Consider raising efavirenz dose to 800 mg/day if patient wt >60 kg	Therapeutic drug monitoring may be warranted to avoid toxicity	39, 40, 157, 196
Etravirine	No information available, likely significant ↓ AUC and ↓ C_{max}	Contraindicated		134
Nevirapine	↓ AUC 46%, ↓ C_{max} 42%, ↓ C_{min} 53%	Contraindicated	Failure of therapy	35, 207
CCR5 antagonist				
Maraviroc	Ratio of maraviroc PK parameters with rifampin to those without rifampin was C_{min} of 0.22 (90% CI, 0.17–0.28), AUC of 0.368 (90% CI, 0.328–0.413), and C_{max} of 0.335 (90% CI, 0.260–0.431)	If used without a strong CYP3A inhibitor, raise maraviroc dose to 600 mg p.i. b.i.d. If used with a strong CYP3A inhibitor, 300 mg p.o. b.i.d.	Must balance with ritonavir usage	271
Integrase inhibitor				
Raltegravir	↓ AUC 40%, ↓ C_{max} 38%, ↓ C_{min} 61%	Consider raising raltegravir dose to 800 mg p.o. b.i.d.		52
Protease inhibitors				
Amprenavir	↓ AUC 82%, ↓ C_{max} 70%, ↓ C_{min} 92%	Contraindicated	No longer formulated	203
Atazanavir	↓ AUC 53%, ↓ C_{max} 72%, ↓ C_{min} 98%	Contraindicated	Ritonavir does not improve levels	2, 111, 161
Darunavir	No information available, likely significant ↓ AUC and ↓ C_{max}	Contraindicated		166
Fosamprenavir	Administration with amprenavir; ↓ AUC 82%, ↓ C_{max} 70%, ↓ C_{min} 92%	Contraindicated	Prodrug of amprenavir	203
Indinavir	↓ AUC 92%, ↓ C_{max} 87%	Contraindicated		42, 136
Lopinavir-ritonavir	Concentrations of lopinavir, ↓ AUC 75%, ↓ C_{min} 99%	Contraindicated	Ritonavir boosting did not increase levels	166, 209
Nelfinavir	↓ AUC 83%, ↓ C_{max} 76%	Contraindicated		142
Ritonavir	↓ AUC 35%, ↓ C_{max} 25%, ↓ C_{min} 49%	Contraindicated		166, 209
Saquinavir	↓ AUC 70%, ↓ C_{max} 65%	Contraindicated	Ritonavir boosting did not increase levels	210
Tipranavir	No information available; likely significant ↓ AUC and ↓ C_{max}	Contraindicated		142

[a] Abbreviations: AUC, area under curve; C_{max}, concentration maximum; C_{min}, concentration minimum; p.o., oral; CL, clearance; C_{ss}, steady-state concentration; i.v., intravenous; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PK, pharmacokinetic; ↑, increase; ↓, decrease.

tion therapy with other antibiotics for staphylococcal infections is discussed below.

(ii) β-Lactams. The combinations of rifampin with β-lactam antibiotics, especially nafcillin, oxacillin, and cephalothin, have been the most frequently studied *in vitro* combinations for the treatment of MSSA infections (199). Tuazon et al. evaluated the nafcillin-rifampin combination against 20 strains of MSSA from patients with endocarditis (246). A microtiter checkerboard dilution method was used to determine the MICs and MBCs of the drugs used either alone or in combination. Their definitions of synergy were not standardized with other *in vitro* studies, as they had a category of "partial synergy" and "indif-

TABLE 3. Rifampin combination antimicrobial *in vitro* and *in vivo* studies[a]

Subject and author(s) (reference)	Combined antibiotic(s)	Organism(s)	*In vitro*			*In vivo*		
			Method	Interaction	Outcome	Animal	Infection	Outcome
Antistaphylococcal penicillins								
Sande and Johnson (219)	Penicillin	MSSA				Rabbit	Endocarditis	Rifampin resistance emerged
Zinner et al. (281)	Methicillin-oxacillin	MSSA/MRSA	TK/CB SBA	A, S	A at high-dose oxacillin, S at low-dose oxacillin			
Watanakunakorn and Tisone (262)	Nafcillin, oxacillin	MSSA	TK	A, I	No S seen			
Maduri et al. (160)	Oxacillin	MSSA, MRSA	CB, TK, SBA	A, I	Most isolates A; at low doses, S or I			
Hackbarth et al. (112)	Nafillin	MSSA	SBA	A	Reduced activity			
Cehpalosporins								
Zinner et al. (281)	Cephalothin	MSSA/MRSA	TK/CB SBA	A	No benefit			
Norden (185)	Cephalothin	MSSA				Rabbits	Osteomyelitis	Rifampin resistance emerged; other antibiotics sensitive
Brandt et al. (37)	Cefazolin	MSSA				Rabbit	Endocarditis	Antagonism with concentrations above MIC
Brandt et al. (36)	Cefazolin, cefpirome	CoNS				Rabbit	Endocarditis	Not predictive; better than monotherapy
Cormican et al. (56)	Cefotaxime	PRSP				Rabbit	CSF	Reduced activity with combination
Gordon et al. (107)	Cefotaxime, ceftazidime, cefuroxime, ceftriaxone	*Haemophilus influenzae*	TK	S	Greater than MIC			
Ribes et al. (211)	Ceftriaxone	PRSP	TK	A	When subinhibitory concentrations used; resistance to rifampin	Rabbit	Meningitis	Improved efficacy when combined
Suntur et al. (236)	Ceftriaxone	PRSP				Rabbit	Meningitis	Combination as good as ceftriaxone and vancomycin
Valdes (248)	Cefpirome, ceftazadime	*Pseudomonas*	FIC agar dilution	S	Bactericidal effect greater when given early in incubation			
Vancomycin								
Bayer and Morrison (26)	Vancomycin	MRSA, MSSA	TK, CB	I or S, TK; A, CB	Most I by TK; S late phenomenon; all A by CB			
Bayer and Lam (25)	Vancomycin	MRSA				Rabbit	Endocarditis	No evidence of antagonism
Lowy et al. (158)	Vancomycin and gentamicin	CoNS	TK	S	Rifampin-resistant strains when used with vancomycin			
Tuazon et al. (246)	Vancomycin	MSSA	MBC	I, S	5/20 synergistic			
Van der Auwera and Joly (251)	Vancomycin	MSSA, MRSA	MBC	S	Variable results			
Watanakunacorn and Guerriero (261)	Vancomycin	MSSA	TK	A	43 of 50 antagonistic			
Stein and Libertin (232)	Vancomycin	Nutritionally variant streptococci	TK	S				
Norden and Shaffer (187)	Vancomycin	MSSA				Rabbits	Osteomyelitis	85% effective sensitive
Quinolones								
Hessen et al. (119)	Temfloxacin	MRSA				Rabbit	Endocarditis	Significant reduction in bacterial counts
Dworkin et al. (73)	Ciprofloxacin, perfloxacin	MRSA				Rat	Osteomyelitis	Combinations better than monotherapy
Kaatz et al. (137)	Ciprofloxacin	MSSA				Rabbit	Endocarditis	Unpredictable, but combination had fewer resistant isolates emerge
Henry (117)	Ciprofloxacin	MRSA				Rats	Osteomyelitis	Most effective; rifampin resistance in vancomycin group
Baltch et al. (18)	Levofloxacin	*Legionella pneumophila*	TK	S	Only antibiotic of group			
Havlichek (114)	Ciprofloxacin	*Legionella pneumophila*				Guinea pigs	Intraperitoneal	No advantage over monotherapy

Linezolid								
Baldoni et al. (16)	Linezolid	MRSA				Guinea pigs	Foreign body	Improved killing combined
Grohs et al. (110)	Linezolid	MRSA	TK	I				
Jacqueline et al. (128)	Linezolid	MRSA	TK	A	Most active			
Tsaganos et al. (243)	Linezolid	MRSA				Rabbit	Endocarditis	Increased cidality in lungs
Dailey et al. (62)	Linezolid	MRSA				Rabbit	Endocarditis	Indifference
Daptomycin								
Credito et al. (59)	Daptomycin, gentamicin	MRSA, hVISA	TK	S	All isolates			
Khasawneh et al. (143)	Daptomycin	MRSA	TK	I, A	No benefit if rifampin resistant initially			
Sakoulos et al. (217)	Daptomycin	MRSA				Rats	Endocarditis	Combination statistically better than daptomycin alone
Rand (208)	Daptomycin	VRE	Etest MICs	I	No benefit with novel method			
Pankey (191)	Daptomycin	VRE	TK, Etest	S, I	75% isolates synergistic			
Other antimicrobials								
Zinner et al. (281)	Minocycline	MSSA	CB	S	*In vitro* synergy			
Segreti et al. (224)	Minocycline	MSSA, MRSA, CoNS	MBC	I, S	About 30% synergy			
Hackbarth et al. (112)	Erythromycin, clindamycin, trimethoprim	MSSA	SBA	S	Resistance emerges with trimethoprim			
Watanakunakorn (260)	Clindamycin	MSSA	TK	S, I	Only for clindamycin-sensitive strains			
Harvey (113)	Trimethoprim	*Klebsiella, Enterococcus faecalis*	TK	A				
Zarrouk et al. (273)	Quinupristin-dalfopristin	MSSA	TK	I	Rifampin resistance emerged	Rabbit	Endocarditis	Highly synergistic compared to *in vitro*

[a] Abbreviations: TK, time-kill; CB, checkerboard; SBA, serum bactericidal activity; FIC, fractional inhibitory concentration; MBC, minimal bactericidal concentration; S, synergy; A, antagonism; I, indeterminate (additive); MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*; hVISA, heteroresistant vancomycin-intermediate *S. aureus*; CoNS, coagulase-negative staphylococci; PSSP, penicillin-sensitive *Streptococcus pneumoniae*; PRSP, penicillin-resistant *S. pneumoniae*; VRE, vancomycin-resistant enterococci.

ference" based on the combination of the drug's relationship to the MBC of the individual drugs (246). Those authors reported "full synergy" for 3 of the 20 (15%) isolates and partial synergy for 9 (45%) other isolates with the rifampin-nafcillin combination (246).

Zinner et al. assessed that the rifampin-oxacillin combination had "enhanced" killing at subinhibitory concentrations; however, the combined effectiveness of the drugs was reduced at higher concentrations of rifampin (281). This paradoxical *in vitro* result would be difficult to implement in clinical practice because one would need to achieve a serum level of rifampin to approach but not be greater than the MBC to achieve an effect over either drug alone. Those authors concluded that the *in vitro* synergy of rifampin combination therapy was infrequent and that the bactericidal activity of rifampin was reduced at high concentrations (281). Maduri et al. replicated those results by showing indifference or antagonism at normal concentrations of the rifampin-oxacillin combination but synergy at subinhibitory concentrations with the rifampin combination against MSSA (160). Brandt et al. demonstrated the same concentration-dependent variability with cephalosporins combined with rifampin (37). Their treatment outcomes with a cephalosporin-rifampin combination were the same as those that Zinner et al. had shown with oxacillin, where the combined therapy made antagonism occur at levels above the MBC (37, 281).

Watanakunakorn and Tisone studied treatment with rifampin combined with oxacillin or nafcillin for 20 MSSA strains by using standard time-kill methodology (262). Those authors could not demonstrate any synergy; however, many of the MSSA strains had the "skip tube" phenomenon, and those authors thus concluded that combination therapy consisting of rifampin with nafcillin or oxacillin should be avoided (262). In contrast, Hackbarth et al. demonstrated that the rifampin-nafcillin combination significant reduced bactericidal activity (112).

Van der Auwera and Klastersky summed up the *in vitro* data for rifampin-oxacillin against *S. aureus* after their results from time-kill and checkerboard studies showed synergy, antagonism, and indifference, stating that "these findings again illustrate the complex and often unpredictable effect of combining rifampin with β-lactam antibiotics" (249).

(iii) Vancomycin. There have been many *in vitro* studies performed for rifampin-vancomycin combination therapy (217). With MSSA isolates, nafcillin combined with rifampin demonstrated superiority to vancomycin in suppressing the emergence of rifampin-resistant isolates (78). Another concern with the rifampin-vancomycin combination is that each drug penetrates tissue differently based on kinetics. For example, vancomycin penetration into lung tissue is not sustained, and the same was seen for the meninges and infected bone, whereas rifampin easily penetrates these tissues (61, 109, 120). The rifampin-vancomycin *in vitro* interaction appears to range from antagonistic to indifferent, with very few synergistic studies (25, 26, 112, 119, 158, 218, 246, 251, 258, 261). Tuazon et al. showed that the rifampin-vancomycin combination had "partial synergism" with only 25% of the MSSA isolates, with the remainder being indifferent, while the nafcillin-rifampin combination had "partial synergism" for 60% of the isolates (246). Watanakunakorn and Guerriero showed antagonism for 43 of 50 *S. aureus* strains using the rifampin-vancomycin combination.

Those authors concluded only that vancomycin may have prevented the resurgence of rifampin-resistant mutants (261). Bayer and Morrison decided that the nature of the *in vitro* bactericidal interactions of rifampin-vancomycin against *S. aureus* could not be established after reporting *in vitro* results of mixed synergy and antagonism (26). Those authors noted that the combination interaction depended upon the synergy technique and test system utilized (26). In conclusion, most *in vitro* studies demonstrated that the rifampin-vancomycin combination demonstrates mostly antagonism or indifference *in vitro* (26, 83, 112, 119, 159, 187, 245, 246, 251, 281), with very few studies showing synergy or additivity (190, 254, 258). Therefore, the *in vitro* testing data do not support the use of rifampin-vancomycin combination therapy for *S. aureus* infection.

(iv) Quinolones. The combination of rifampin with a quinolone for staphylococcal infections offers a great therapeutic option for outpatient therapy. They both have excellent oral bioavailability and safety, allowing them to be used for prolonged courses of therapy. The quinolone-rifampin combinations that have been studied include ciprofloxacin, perfloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin (18, 73, 74, 106, 117, 137, 279).

The *in vitro* results for the rifampin-quinolone combination appear to replicate the β-lactam–rifampin outcomes. Hackbarth et al. found conflicting results when either the ciprofloxacin-rifampin or perfloxacin-rifampin combination was used against MSSA, with additivity being shown by SBA but antagonism being shown by time-kill analysis (112). Similarly, Van der Auwera and Joly also demonstrated that the rifampin-ciprofloxacin *in vitro* combination was antagonistic when the concentration for either drug was above the MIC for *S. aureus* but was additive when subinhibitory concentrations were being utilized (251).

Weinstein et al. evaluated SBA activities of rifampin alone or with ciprofloxacin against MSSA and MRSA isolates in a pharmacokinetic study. Those authors found that the activity of each drug showed antagonism when combined together, yet substantial SBA remained (264). Kang et al. also could not show rifampin-ciprofloxacin *in vitro* synergy, but the addition of rifampin prevented the emergence of ciprofloxacin-resistant *S. aureus* isolates (138). The rifampin-quinolone *in vitro* data suggest that the combination does not appear to offer any substantial benefit against *S. aureus* other than perhaps preventing quinolone resistance.

(v) Linezolid. Linezolid is an oxazolidinone antibiotic with activity against Gram-positive infections, and its excellent oral bioavailability has made it a promising agent for combination therapy with rifampin. The *in vitro* data for linezolid-rifampin treatment of infections caused by *S. aureus* have shown that the effect is additive and prevented the emergence of rifampin-resistant mutants (110, 177). Also, the linezolid-rifampin combination appeared to be very active against MRSA strains (128).

(vi) Daptomycin. Daptomycin is a lipopeptide antibiotic with potent activity against Gram-positive organisms, especially *S. aureus* (90). There is very little *in vitro* information on the rifampin-daptomycin combination, with the only *in vitro* studies reported showing indifference or antagonism when used against MRSA (59, 143).

(vii) Fusidic acid and novobiocin. Although fusidic acid and novobiocin are no longer available in the United States, they may be available elsewhere in the world for use with rifampin, especially for the treatment of complicated staphylococcal infections, in particular MRSA (124). The rifampin-fusidic acid combination appears to demonstrate synergy rather than indifference by several *in vitro* studies (82, 86, 254). The rifampin-novobiocin combination demonstrates synergy or indifference by *in vitro* studies, especially when there are heavy inocula of bacteria (48, 135, 258). Most of the *in vitro* data were reported many years ago, before standards were established for all laboratories, but the results are not discouraging.

(viii) Clindamycin, minocycline, sulfa drugs, and streptogramins. The rifampin-clindamycin combination demonstrated antagonism or indifference *in vitro* (121, 260). The rifampin-trimethoprim-sulfamethoxazole combination was antagonistic *in vitro* against *S. aureus* (113). The rifampin-minocycline combination showed synergy by *in vitro* checkerboard testing, and this combination has been frequently combined for the prevention of catheter-related infections (224). Lastly, the rifampin-quinupristin-dalfopristin combination showed *in vitro* synergism when tested against staphylococci (218, 273).

(ix) Summary of *in vitro* studies. With a review period covering several decades, the *in vitro* data for rifampin combination therapy against staphylococci appear to frequently show antagonism or indifference, with synergy being found inconsistently. An observation from these *in vitro* results is that the addition of rifampin to antibiotics typically regarded as being bactericidal appears to decrease or leave unchanged their bactericidal killing. However, the addition of rifampin to antibiotics generally regarded as being bacteriostatic appears to result in some improved bactericidal activity over either drug alone.

***In vivo* and clinical studies.** *In vivo* models have demonstrated the strongest data for rifampin combination therapy for the treatment of staphylococcal infections compared to clinical studies. The next section will review these data for common staphylococcal disease processes where rifampin combination therapy is used (Table 3).

(i) Native valve endocarditis and bacteremia. *(a) In vivo studies*. Animal models have played a central role in evaluating antimicrobial combinations and translating those results to the clinical setting for the management of endocarditis due to *S. aureus*. These models have been necessary because of the complexity in performing human endocarditis studies (34, 90). Sande and Johnson developed a rabbit endocarditis model to evaluate antibiotic combination effectiveness (219). Those authors demonstrated that the rate at which various antibiotic combinations kill high titers of bacteria in broth correlated with the relative effectiveness of the agents. They showed that the combination of penicillin and gentamicin was both synergistic *in vitro* and more effective in eradicating *S. aureus in vivo* than penicillin alone. However, when those authors compared penicillin to the combination of penicillin and rifampin (35 mg/kg four times a day [q.i.d.] intramuscularly), the combination of penicillin and rifampin was less effective, with the emergence of rifampin-resistant strains. (219) With penicillin-resistant *S. aureus* strains being endemic when this model was developed, it would be difficult to apply this result clinically.

Mandell and Moorman increased the rate of survival of mice

from 40% to 77% ($P < 0.001$) with the rifampin-nafcillin combination using a mouse model of MSSA endocarditis, and there was no development of rifampin-resistant *S. aureus* strains in the combined-therapy group (162).

The animal studies evaluating rifampin-vancomycin combination therapy for MRSA bacteremia and endocarditis have not shown any benefit. Bayer and Morrison compared the combination of vancomycin (30 mg/kg/day) and rifampin (20 mg/kg/day) to each drug alone in a rabbit MRSA endocarditis model. Outcomes were determined by determinations of valvular bacterial CFU, rates of valvular sterilization, and overall cure. In this well-controlled environment, the combination therapy was significantly better in all of these parameters and prevented rifampin resistance (25). However, neither Hessen et al. (rifampin at 12 mg/kg/day with vancomycin) nor Perdikaris et al. (rifampin at 20 mg/kg/day with vancomycin) could demonstrate any improved valvular sterilization with rifampin-vancomycin combination therapy using *in vivo* MRSA endocarditis models (119, 198). Kaatz et al. compared the rifampin (10 mg/kg/day)-ciprofloxacin (25 mg/kg/day) combination to vancomycin in a rabbit MSSA endocarditis model with the end points evaluating CFU of bacteria per vegetation or CFU in the spleen. The rifampin-ciprofloxacin combination had a clearance of bacteria similar to that of vancomycin alone, and the combination also reduced the emergence of ciprofloxacin-resistant strains. However, with regard to efficacy, those authors were concerned with the unpredictable nature of their results (137). Using an MRSA aortic-valve endocarditis rabbit model, Chambers et al. concluded that the combination of levofloxacin (20 mg/kg/day) with rifampin (10 mg/kg/day) was antagonistic *in vitro* and *in vivo* and without any benefit (43). However, Hessen et al. used a rifampin-temafloxacin combination for MRSA endocarditis and reported significant reductions in the CFU within vegetations (119).

When combined with rifampin, daptomycin and linezolid have both shown good *in vivo* activity against *S. aureus*. Sakoulas et al. compared rifampin (25 mg/kg/day)-daptomycin therapy in a rat model of MRSA endocarditis to therapy daptomycin alone, with outcomes determined by residual CFU in vegetations (217). The rifampin-daptomycin combination therapy was significantly better at reducing CFU in the vegetations ($P = 0.006$) (217). Dailey et al. compared rifampin (5 mg/kg every 8 h [q8h])-linezolid combination therapy to linezolid monotherapy with a rabbit model of MSSA endocarditis (62). Those authors also demonstrated significant reductions in valvular CFU with the combination therapy ($P < 0.05$). Using a rabbit MRSA endocarditis model, Tsaganos et al. demonstrated an increased sterility of secondary foci of endocarditis, including pulmonary septic emboli, with linezolid-rifampin combination therapy (243). Zarrouk et al. demonstrated significant CFU reductions ($P < 0.001$) with rifampin (10 mg/kg q8h)-quinupristin-dalfopristin combination therapy over monotherapy in a rabbit model of *S. aureus* endocarditis (273).

The described *in vivo* data for rifampin combination therapy for *S. aureus* endocarditis have several limitations that affect whether the results could be applied clinically. The animals are in a controlled environment where the organism burden is predetermined, the duration of bacteremia is known, and animal sacrifice occurs within a few days of infection, and outcomes are determined by valvular colony counts rather than clinical outcome. Another problem is that rifampin dosing and the route by which therapy is given are different in all the studies, thus making comparisons between studies and to the clinical setting almost impossible. The only antibiotics in combination with rifampin that appeared to have a significant effect *in vivo* were daptomycin and linezolid.

(b) Clinical studies. The reasons for considering rifampin combination therapy for native valve endocarditis (NVE) are (i) that it is highly active against *S. aureus*, (ii) that it has good tissue and vegetation penetration, and (iii) that oral therapy can be used to discharge intravenous drug users early from hospital (57, 74, 237). However, what has not been defined are the timing of the addition of rifampin to the other antibiotic in relation to bacteremia, the appropriate dose and interval of rifampin needed, how long therapy should be maintained once initiated, and patient adherence to therapy if being managed as an outpatient (57, 74, 163, 227). With increasing rates of MRSA causing NVE, especially strains with heteroresistance to vancomycin (heteroresistant vancomycin-intermediate *S. aureus* [hVISA]) and frequently causing prolonged bacteremia, clinicians have few choices when monotherapy is failing (28, 57, 90, 163) (Table 4).

The consideration of rifampin combination therapy for the treatment of NVE due to MSSA originated over 40 years earlier with case reports of successful outcomes for 4 patients with MSSA septicemia (23, 130, 194). Suter et al. reported the successful treatment of 2 heroin addicts, one with left-sided endocarditis caused by MSSA and the other with septic pulmonary emboli from tricuspid valve endocarditis due to MSSA with a combination of methicillin with aminoglycoside and rifampin at 20 mg/kg/day (237). Tebas et al. showed that rifampin-ciprofloxacin combination therapy was associated with the early emergence of rifampin resistance when treating MSSA endocarditis (241). Separately, there is a case report of rifampin-levofloxacin combination therapy successfully treating MSSA endocarditis with an annular abscess without surgery (87). However, most case reports of rifampin combination therapy are for the management of MRSA endocarditis. Simon et al. used rifampin-vancomycin combination therapy for MRSA endocarditis where both cases clinically failed and subsequently developed rifampin resistance (227). Bennett et al. presented a case with MRSA bacteremia that received vancomycin initially and then had rifampin added while the patient was bacteremic, and therapy was later changed to daptomycin and gentamicin treatment. The patient subsequently developed diminished susceptibility to vancomycin, daptomycin, and gentamicin and rifampin resistance because control of the source of MRSA infection could not be obtained (28). Lastly, there was a successful treatment of persistent MRSA bacteremia with metastatic foci by using rifampin-linezolid combination therapy (223). The standard limitations of case reports of reporting and publication bias affect any conclusions from these cases.

Riedel et al. performed a retrospective, matched-cohort study comparing 42 cases who had received rifampin combination therapy to 42 controls who had not for NVE caused by *S. aureus*. Those authors found that there were similar clinical outcomes between the two groups; however, the addition of rifampin appeared to prolong the duration of bacteremia. The rifampin com-

TABLE 4. Significant clinical studies of rifampin combination therapy[a]

Disease and authors (reference)	Study design	No. of cases	Organism(s)	Antibiotic(s)	Outcome	Rifampin resistance
Prosthetic valve endocarditis						
Karchmer et al. (141)	Retrospective	75	CoNS	Nafcillin +/− gentamicin	10/20 cured; poorer response than vancomycin	N
				Vancomycin +/− gentamicin	21/26	N
Karchmer et al. (140)	Retrospective	23	CoNS	Vancomycin +/− gentamicin	16/23 cured	Y (2 cases)
Prosthetic joint infections						
Zimmerli et al. (279)	Prospective, randomized	33	MSSA	Ciprofloxacin	12/12 cured vs 7/12	N
Barberán et al. (21)	Retrospective	25	MSSA, CoNS	Levofloxacin	18/25 cured	N
Laffer et al. (153)	Retrospective	35	MSSA (14/33)	Multiple	92% success	N
Choong et al. (47)	Retrospective	14	Multiple	Quinolone	Salvage therapy effective	N
Aboltins et al. (1)	Retrospective	20	MSSA/MRSA	Ciprofloxacin	10/11 MRSA responded	N
Berdal et al. (29)	Retrospective	29	MSSA (18/29)	Fusidic acid	24/29 successful	NT
Donaldson et al. (69)	Retrospective	2	MRSA	Ciprofloxacin	Failed	Y
Barberán et al. (20)	Retrospective	60	CoNS, MRSA	Fusidic acid	Higher MRSA failure rate	N
Chronic osteomyelitis						
Norden et al. (186)	Retrospective	28	MSSA	Nafcillin	70% cure	N
Senneville et al. (226)	Retrospective	20	MSSA	Ofloxacin	88.2% cure	N
Senneville et al. (225)	Retrospective	50	Mixed	Quinolone	2/4 MRSA cases failed therapy	NT
Daver et al. (65)	Retrospective	72	MRSA/MSSA	Vancomycin	MRSA cases responded poorly (65%) vs MRSA cases (83%)	Y
Native valve endocarditis						
Van der Auwera et al. (250)	Double blind, placebo	33	MSSA	Nafcillin	61% vs 56% (placebo), 3 vs 28% bacteriological failure in placebo	N
Swanberg and Tuazon (238)	Retrospective	8	MSSA/CoNS	Nafcillin, cephalothin, vancomycin	Correlation with SBA and outcome	N
Levine et al. (155)	Prospective, randomized	21	MRSA	Vancomyicn	Increased duration of bacteremia (8 days vs 7)	N
Falcone et al. (80)	Retrospective	4	*Staphylococcus haemolyticus*	Vancomycin	2 patients cured, 1 surgery, 1 died	N
Riedel et al. (214)	Retrospective	42	MSSA/MRSA	Vancomycin, nafcillin	Increased hepatotoxicity; no improved outcomes	Y (22%)
Maor et al. (163)	Retrospective, case-control	27	hVISA	Vancomycin	Prolonged bacteremia, increased complications	Y (44%)
Catheter infections						
Raad et al. (204)	Multicenter, randomized	147	MSSA/CoNS	Minocycline	No infections in coated vs 7 ($P = 0.001$)	N
Swanberg and Tuazon (238)	Retrospective	8	MSSA/CoNS	Nafcillin, cephalothin, vancomycin	Correlation with SBA and outcome	N
Resistant Gram-negative infections						
Saballs et al. (215)	Pilot study	10	Carbapenem-resistant *Acinetobacter*	Imipenem	3 deaths, 2 microbiological failures	Y
Tascini et al. (239)	Retrospective	8	MDR *Pseudomonas*	Colistin	6 cure, 2 failed microbiologically or intolerance	N
Bassetti et al. (22)	Prospective	29	MDR *Acinetobacter*	Colistin	22/29 (76%) had a response, 10% nephrotoxicity	N
Mataouakkil et al. (176)	Observational	26	MDR *Acinetobacter*	Colistin	Good response, including 9 bacteremic patients	N

[a] Abbreviations: Y, yes; N, no; NT, not told; +/−, with or without; SBA, serum bactericidal activity; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*; hVISA, heteroresistant vancomycin-intermediate *S. aureus*; CoNS, coagulase-negative staphylococci; MDR, multidrug resistant.

bination group had a higher severity of illness and more left-sided endocarditis. Importantly, rifampin resistance isolates developed in 22% of the cases, and all these occurred when the patients had their rifampin therapy started during ongoing bacteremia (214). That review also found that hepatitis C virus (HCV)-infected patients were at a greater risk of developing hepatotoxicity with rifampin combination therapy. Also, drug interactions, especially to protease inhibitors, were frequently missed by clinicians when rifampin was initiated (214). Jang et al. retrospectively reviewed data from patients with prolonged MRSA bacteremia at their institution from 2006 to 2008. Those authors reported 6 patients treated with the vancomycin-rifampin combination, with two patients having some early microbial clearance, but none were salvageable by the end of therapy for their infection. Two of the patients receiving rifampin combination therapy had prosthetic valve endocarditis caused by MRSA, and both died (129).

The emergence of MRSA strains with elevated MICs of vancomycin ($\geq$2 μg/ml) or hVISA strains was associated with worse clinical outcomes because the therapeutic vancomycin levels required for a successful response have been associated with toxicity (57, 120). Maor et al. retrospectively studied 27 patients with hVISA bacteremia compared to 223 patients with MRSA bacteremia. Those authors found that patients with hVISA bacteremia were more likely to have prolonged bacter-

emia (12 versus 2 days), endocarditis (18.5% versus 3.6%; $P = 0.007$), and an emergence of rifampin resistance while on therapy (44% versus 5.9%) (163). The suggested mechanism for rifampin resistance with these hVISA isolates was vancomycin serum levels that were below the hVISA MIC while rifampin was coadministered during the initial bacteremia. This was effectively delivering rifampin monotherapy to patients with a high burden of disease (163). Howden et al. presented a case series of 17 patients with hVISA bacteremia or endocarditis who had failed vancomycin therapy. Seven of these patients were treated with rifampin-fusidic acid combination therapy: five of them died, and only one patient had surgical intervention (124). The retrospective clinical data for the role of rifampin combination therapy in the management of *S. aureus* bacteremia and endocarditis are concerning for treatment failures and the emergence of rifampin resistance strains, especially when used with vancomycin for the treatment of MRSA. The main theme from this review is that the addition of rifampin to the treatment of active *S. aureus* bacteremia or without proper source control (i.e., surgery) does not improve clinical outcomes and results in the emergence of rifampin resistance.

There are five prospective clinical studies evaluating rifampin combination therapies for *S. aureus* bacteremia and NVE, with three of the five studies evaluating right-sided endocarditis (74, 115, 155, 222, 250). Dworkin et al. performed a nonrandomized prospective cohort study that initially started with intravenous rifampin (600 mg twice a day [b.i.d.])-ciprofloxacin combination therapy that was then changed to oral combination therapy for the treatment of right-sided endocarditis caused by *S. aureus* in intravenous drug users (74). All 10 patients that completed therapy had bacteria cleared from blood cultures at 4 weeks; however, 4 patients did not complete therapy due to nonadherence, a concern for outpatient endocarditis therapy (74). Subsequently, two larger prospective studies evaluated the role of oral quinolone-rifampin therapy in right-sided endocarditis (115, 222). Heldman et al. performed a prospective, randomized, unblinded trial comparing ciprofloxacin (750 mg b.i.d.) and rifampin (300 mg b.i.d.) to intravenous oxacillin or vancomycin plus gentamicin for 5 days for patients with right-sided endocarditis. There were 85 patients with right-sided endocarditis that enrolled in the study, only 44 (52%) (19 patients given drug orally and 25 patients given drug intravenously) of whom completed inpatient and follow-up evaluations. Of these 44 patients, 95% of the patients had *S. aureus* bacteremia, with MRSA being the causative organism for only 5 of these patients. There were 4 clinical failures: 1 of the 19 patients (5%) in the combination therapy group and 3 of the 25 (12%) patients in the intravenous therapy group ($P > 0.05$) (115). Those authors suggested that for selected patients, the rifampin-ciprofloxacin combination was safe and effective for right-sided endocarditis; however, it should be noted that barely half the patients enrolled completed the study (115).

Schrenzel et al. performed a multicenter, randomized clinical study comparing fleroxacin-rifampin combination therapy to standard therapy (222). Rifampin was given at 600 mg daily, and the study included catheter-related and secondary bacteremias, but those authors noted that only 2 of the 104 patients had MRSA bacteremia. The overall microbiological (86% versus 84%, respectively) and clinical (82% versus 80%, respectively) efficacies were similar between the two groups, but there were significant adverse events in the combination therapy group, including hepatitis, rash, and neurotoxicity (222). That study had several large methodological flaws, which affect result interpretations; these include allowing for a 30% difference between the groups to show "equivalence," underpowering the study, and the finding that all of the 95% confidence intervals exceed the prehoc range of 30%, which raises a concern that the combined therapy had no effect or was worse than standard therapy (101, 213).

Van der Auwera et al. performed a double-blind, placebo-controlled study comparing oxacillin (1,200 g/day) or vancomycin (2 g/day) plus rifampin (1,200 mg/day) to oxacillin or vancomycin plus placebo for complicated *S. aureus* infections (250). Of the 65 patients with *S. aureus* infection, 29 had bacteremia (13 in the combination therapy group), but again, only 4 had MRSA. Evaluating the bacteremic patients, 9 of 13 (69%) in the combination group and 10 of 16 (63%) in the placebo group had clinical cure. Although there was no difference in clinical outcomes, there was no emergence of rifampin-resistant mutants in the treatment failure group (250).

Levine et al. performed a cohort randomized study of 42 consecutive patients with NVE caused MRSA comparing vancomycin and rifampin (600 mg daily for 28 days) to vancomycin alone. The vancomycin-rifampin combination prolonged MRSA bacteremia by a day (8 versus 7 days; $P > 0.05$), but with wide confidence intervals and small numbers, this is not a definitive result (155). This is the only prospective study of NVE and rifampin-vancomycin combination therapy.

Lastly, there are several case reports of vancomycin-rifampin combination therapy successfully treating NVE caused by *Staphylococcus haemolyticus* and *Staphylococcus lugdunensis* (80, 103, 200).

There are limited *in vivo* and clinical data on rifampin combination therapy for the treatment of *S. aureus* NVE and bacteremia. With increasing rates of MRSA (92), the rifampin-vancomycin combination for MRSA bacteremia and endocarditis had significant clinical failure, with the emergence of rifampin resistance. This combination appears to be an unfavorable treatment option, and until the issues of when to initiate rifampin (dosing and clearance of bacteremia) can be defined, alternative antibiotics should be considered. The data from this review support the current American Heart Association (AHA) endocarditis guidelines, which do not recommend the addition of rifampin for the treatment of NVE caused by *S. aureus* (15).

(ii) Biofilms. The ability of rifampin to enter cells is its most important mechanism of intracellular killing of tuberculosis (220). This major ability of rifampin to penetrate into cells and biofilms to treat infections is supported by strong clinical data for prosthetic material infections. Biofilms occur when microbes attach to any implanted prosthetic material. A biofilm has been defined as "a structured community of bacterial cells enclosed in a self-produced polymeric matrix adherent to an inert or living surface" (58). Bacteria within these biofilms are associated with little turnover and communicate with each other using small molecules in a process called "quorum sensing" (58, 256). The bacteria within these biofilms are 100 to

1,000 times less susceptible to antibiotics than their planktonic (or free-growing) forms that are cultured on plates, making them difficult to treat (58, 70).

(a) In vitro and in vivo data. Rifampin achieves high concentrations within neutrophils, endothelial cells, macrophages, and biofilms and has improved activity in combination with another antibiotic compared to that if it is used alone (19, 64, 195, 216). Saginur et al. demonstrated that the addition of rifampin to the treatment of *S. epidermidis* and MRSA biofilm infections resulted in improved antimicrobial susceptibility to other antimicrobials compared to that if used alone. Those authors showed that rifampin reduced the adherence of the organisms within the biofilm to the foreign material, allowing the active agent to then work (216). Those observations were supported by data showing that ciprofloxacin alone failed to eradicate stationary-phase *S. epidermidis* foreign-body infection, but all patients responded when rifampin was added to the treatment regimen (266). Darouiche et al. showed that despite vancomycin achieving adequate levels within the biofilm, it appeared to have a diminished effect on stationary-phase bacteria within the biofilm (63). Zimmerli et al. showed that rifampin combination therapy for infection of prosthetic material was superior ($P < 0.001$) to monotherapy and that the drug efficacy could be predicted if the stationary-phase MBC was in the sensitive range for the combined antibiotics rather than the antibiotic trough level exceeding the MIC (276). Chuard et al. demonstrated that rifampin-fleroxacin combination therapy could significantly reduce MRSA infection over 3 weeks in an experimental animal model without the emergence of rifampin resistance isolates and, in some cases, could cure the infection (51).

Hermsen et al. showed that daptomycin was able to remain bactericidal compared to other cell wall-active agents in a peritoneal dialysate medium that compromised the cidality of cell wall-active agents (118). John et al. used rifampin with high-dose daptomycin (equal to 6 mg/kg for humans) for MRSA prosthetic joint infections and found a cure rate of 67% compared to vancomycin (8%) and linezolid (0%) treatment, which prevented the emergence of rifampin-resistant isolates (132). The same group showed a cure rate of 60% when they used the rifampin-linezolid combination, but this was less than that for the levofloxacin-rifampin combination (91% cure) (16). Raad et al. evaluated daptomycin, tigecycline, and linezolid catheter lock solutions against MRSA biofilms and found that daptomycin, tigecycline, and minocycline either alone or in combination with rifampin were superior to vancomycin or linezolid for eradicating biofilms (206). However, vancomycin either with or without rifampin for antibiotic lock therapy was ineffective (206).

Results for rifampin combination therapy *in vitro* and *in vivo* suggest that it is beneficial for the treatment of staphylococcal infections of prosthetic materials, in particular CoNS. Penetration of rifampin into the biofilms and low organism burden have been demonstrated. The rifampin-vancomycin combination was the least efficacious based on *in vitro* and *in vivo* data, while daptomycin appeared to be more effective.

(b) Clinical data. The minocycline-rifampin combination in impregnated central venous catheters to prevent staphylococcal biofilm infections has proven to be very successful (79, 204, 205). This antibiotic combination has been extensively studied, with a recent meta-analysis of randomized controlled studies showing that these impregnated catheters resulted in fewer catheter-related bloodstream infections (CR-BSI) (odds ratio [OR] = 0.23) and less colonization (OR = 0.46) than for nonimpregnated catheters (79, 205). Rifampin resistance also did not occur using these catheters, and this may be a cost-effective approach to the prevention of infections for patients who require intravenous catheters for a prolonged time (79, 205). Importantly, the combination of antibiotics is within the catheter and not infused separately.

With peritoneal dialysis catheters, several small case reports have shown success with rifampin-vancomycin combination therapy for the preservation of the catheter with a CoNS infection (96, 280).

The use of rifampin combination therapy for the treatment of *S. epidermidis* prosthetic valve endocarditis (PVE) is the recommended treatment for this biofilm infection.

Archer et al. described the first successful treatment of a patient with *S. epidermidis* aortic-valve endocarditis with a combination of rifampin, nafcillin, and gentamicin (8). The patient initially had surgical debridement of the valve and was progressing well with treatment with nafcillin and gentamicin. However, the serum bactericidal titers could not achieve the therapeutic range, and the patient had developed ototoxicity after 2 weeks of gentamicin treatment. The gentamicin treatment was stopped, and rifampin at 600 mg b.i.d. was added to the nafcillin treatment, which increased the serum bactericidal titers 16-fold, and the patient had a successful response without rifampin resistance emerging (8).

Several other case reports showed successful therapy with the addition of rifampin to other antibiotics, mostly vancomycin for the treatment of PVE; however, most cases required concomitant surgical intervention (10, 53, 100, 231). One PVE case series reported the emergence of rifampin-resistant *S. epidermidis* strains in 3 patients being treated with vancomycin and rifampin (44). All patients needed surgery after failing combination therapy, which enhances concerns about when to initiate the addition of rifampin therapy with regard to the clearance of blood cultures and duration of antimicrobial treatment without surgery (44).

There are numerous other case reports of PVE caused by various organisms including *Kytococcus schroeteri* and other uncommon organisms that were reported to be successfully treated with rifampin combination therapy (3, 147, 169).

The largest study supporting the use of rifampin combination therapy for PVE was a retrospective analysis of 75 episodes for 55 patients with *S. epidermidis* infection (141). Twenty-one of 26 patients with methicillin-resistant *S. epidermidis* infection were successfully cured with the rifampin (900 to 1,200 mg/day)-vancomycin combination (with or without gentamicin), while only 10 of 20 patients with methicillin-susceptible strains were cured with a rifampin–β-lactam antibiotic combination (with or without gentamicin) (141). Surgery was required for most patients, improving the cure rate. The poor response of the rifampin–β-lactam antibiotic combination was due mostly to the emergence of methicillin-resistant CoNS subpopulations (141). A subsequent retrospective study from those authors specifically evaluating rifampin combination therapy for 23 patients with methicillin-resistant *S. epidermidis* PVE infection using rifampin (900 to 1,200 mg daily) showed a

75% success rate, but 2 rifampin-resistant strains emerged in patients with persistent infection (140). Therefore, from these data, the American Heart Association (AHA) recommended that for the treatment of *S. epidermidis* PVE, treatment should start with vancomycin, rifampin (900 mg/day), and gentamicin for 2 weeks, followed by vancomycin and rifampin for at least 4 further weeks, and surgical intervention should always be considered (15, 139). The recommendations are also the same for PVE caused by *S. aureus* because of the high rate of mortality caused by this infection (133). The committee emphasized that their recommendations are based on data for PVE due to CoNS and from results of animal studies of infected devices, as there are no clinical data (15, 51). With MRSA being a serious cause of PVE and due to reported therapeutic failures with vancomycin and rifampin treatment (124, 129), other antimicrobial combinations such as daptomycin with rifampin may need to be considered. Regardless of the antibiotic combination, surgical therapy should be the mainstay of therapy for PVE due to *S. aureus*.

Prosthetic joint infections can occur early or late after surgery but are associated with significant costs and morbidity (278). The benefits of the addition of rifampin to standard antimicrobial therapy are the intracellular killing of the staphylococci and overcoming the local granulocyte defect caused by the prosthesis that allows the organism to reside within (19, 64, 277). A summary of the clinical data for the use of rifampin combination therapy for prosthetic joint infection (PJI) is shown in Table 4 (1, 21, 29, 38, 47, 69, 149, 153, 279).

It was suggested that quinolone-rifampin combination therapy could be useful for the treatment of PJI (66). Widmer et al. presented a sentinel study to demonstrate the benefit of rifampin combination therapy for orthopedic implant infections (267). Their open-label study evaluated 11 patients who had prosthetic hardware that could not be removed and that was infected with staphylococci or streptococci. All patients received a rifampin combination-based regimen, and there was an 82% success rate, with some improved benefit from the ciprofloxacin-rifampin combination (267). Subsequently, most case series occurred after the large randomized study using rifampin-ciprofloxacin for staphylococcal PJI (279). Berdal et al. used the rifampin-ciprofloxacin combination for 3 months for 29 patients with staphylococcal PJI and reported only 5 failures with an almost 2-year follow-up (29). Rifampin-levofloxacin therapy was also very successful for a series of 25 cases of patients with PJI, 14 of which were caused by CoNS and 11 of which were caused by *S. aureus* (21). Lastly, two other case series also showed that the rifampin-fusidic acid combination was able to salvage patients with PJI (1, 47). Other case reports have similarly shown the success of combination therapy (5, 149).

Most of the case studies of rifampin combination therapy have been done for the treatment of PJI due to MSSA and CoNS. However, a case series by Barberán et al. found that when conserving prosthetic orthopedic material, they had a higher antibiotic failure rate for the treatment of MRSA infections when vancomycin and rifampin therapies were combined (20). Another report described the emergence of rifampin-resistant MRSA strains in two patients given either vancomycin or fusidic acid with rifampin (69).

Zimmerli et al. performed a randomized, placebo-controlled prospective study of initial joint debridement, which was then followed by 2 weeks of intravenous vancomycin or flucloxacillin therapy with either rifampin or placebo (279). This was then followed with long-term oral therapy with either ciprofloxacin-rifampin or ciprofloxacin-placebo. The cure end points were a C-reactive protein level of $\leq$5 mg/liter, a lack of signs and symptoms of infection, and an absence of joint loosening upon imaging at 24 months. There were 24 of the 33 patients enrolled who completed therapy. Twelve of 12 patients were cured in the rifampin-ciprofloxacin group, compared to 7/12 (58%) in the ciprofloxacin-placebo group ($P = 0.02$). Adverse drug reactions included rash and nausea and were the main reason for the discontinuation of therapy for 6 of the 9 nonevaluable patients, which were caused mostly by rifampin. The limitations of that study were as follows: there were no MRSA infections, the ciprofloxacin-resistant isolates were *S. epidermidis* strains, and the sample size was small (279). However, that study provided the strongest evidence supporting rifampin combination therapy for the treatment of PJI due to *S. aureus* provided that there is initial debridement of the infected joint.

There are significantly strong clinical data supporting rifampin combination antimicrobial therapy for the treatment of PJI in conjunction with joint debridement, especially with MSSA and CoNS infections. The use of a rifampin-quinolone combination for salvaging PJI infections due to MSSA is supported by data from a placebo-controlled trial and clinical observations. However, the rifampin-vancomycin combination for PJI due to MRSA has a high clinical and microbiological failure rate and reconfirms the poor responses of this combination as demonstrated by *in vitro* and *in vivo* models.

Osteomyelitis is a complicated disease to diagnose and manage. *S. aureus* accounts for 80% of infections, and it can invade and persist within osteoblasts, thereby becoming difficult to eradicate within hours of invasion (77). There are a few small studies that evaluated rifampin combination therapy for the treatment of chronic osteomyelitis, but they had small numbers of patients.

Aspinall et al. evaluated rifampin combination therapy for a patient with recurrent chronic spinal osteomyelitis with MRSA (12). Using serum bactericidal and inhibition titers of $>$1:1,024 with a combination of rifampin, vancomycin, and gentamicin, those authors were able to treat a deep-seated infection and avoid surgery (12). In a retrospective study, Senneville et al. reviewed the role of 6 months of rifampin-oxacillin therapy for 20 patients with diabetic osteomyelitis and found an 88.2% cure rate. That study used only 10 MSSA isolates and no MRSA isolates, and 47% of the patients had to have their rifampin dosage halved because of intolerability (226). Daver et al. retrospectively reviewed data from patients with *S. aureus* osteomyelitis at 6 months after treatment (65). An important observation was that the cohort with MRSA that received the rifampin-vancomycin combination had significantly worse microbiological and clinical outcomes ($P < 0.02$) than those for any other rifampin combinations (65). Although the penetration of vancomycin into healthy bone is greater than the MIC of most staphylococci, its penetration may be less than the MIC when there is osteomyelitis present and may thus result in rifampin monotherapy (109, 229).

There has been only one prospective clinical study of rifampin combination therapy for chronic osteomyelitis. Norden

et al. performed a randomized, prospective trial comparing nafcillin to nafcillin and rifampin, followed by its combination with other oral antibiotics. Of the 28 patients studied, 70% receiving the rifampin combination experienced cure, while the remainder failed because of inadequate tissue debridement (186).

There is a lack of compelling clinical information to support the use of rifampin combination therapy for osteomyelitis. Another important observation was that the vancomycin-rifampin combination for the treatment of osteomyelitis due to MRSA was again associated with clinical failure (65). Unfortunately, the published literature on the diagnosis, treatment, and management of osteomyelitis is inadequate to make any conclusions about antibiotic therapy in general (154).

Ventricular and spinal shunt infections are associated with significant morbidity and mortality (31). CoNS cause the majority of these infections, followed by *S. aureus* and *Propionibacterium acnes* (55). Rifampin having very good CSF penetration has made it an important component in the management of these infections (31, 55, 146). Most of the data supporting the use of rifampin combination therapy are based on small case series, mostly with good success (55, 91, 105, 146). Similarly, the prolonged use of rifampin combination therapy without a removal of the source of infection can result in the emergence of rifampin-resistant isolates (55). Shunt infections are serious but are associated with a low organism burden and are in a complicated site; therefore, rifampin combination therapy may have a role until the catheter can be removed or replaced.

Other Diseases

Over the years, rifampin combination antimicrobial therapy has been utilized for other nonstaphylococcal disease processes.

***Streptococcus pneumoniae*.** Rifampin combination therapy has been used for *S. pneumoniae* infections, especially meningitis caused by penicillin-resistant strains (penicillin-resistant *S. pneumoniae* [PRSP]) (56, 211, 236).

(i) *In vitro* and *in vivo* data. The *in vitro* data for the vancomycin-rifampin combination therapy for treatment of *S. pneumoniae* infection using time-kill studies again showed indifference, similarly to *S. aureus* (94). Despite data suggesting that rifampin has poor penetration into the brain, animal studies have had mixed results (56, 179, 211, 236). Using a rabbit model, Nau et al. found that rifampin was significantly less active against *S. pneumoniae* in the CSF than ceftriaxone, with paradoxically less efficacy at higher doses of rifampin (179). Cormican et al. showed in an *in vivo* study that cephalosporin monotherapy was effective and that the addition of rifampin decreased the bactericidal activity of cefotaxime (56). However, 2 separate *in vivo* studies of experimental PRSP meningitis comparing ceftriaxone to combination therapy with rifampin found that rifampin combination therapy was highly effective (211, 236). The addition of rifampin to meropenem did not improve the clearance of PRSP in a guinea pig model (88).

(ii) Clinical data. With the emergence of PRSP strains and concerns about cephalosporin failure in clinical practice for treating meningitis, it has been recommended that therapy with vancomycin and rifampin be given with ceftriaxone pending susceptibility testing (93). This recommendation was based on *in vivo* data and poor responses to cephalosporins by children with meningitis (146, 270). Most of the data for using rifampin combination therapy for pneumococcus were obtained from case reports (123, 189). When treating PRSP, the emergence of rifampin resistance via the *rfoB* gene can occur quickly, and its spread can be tracked through communities (84, 167, 253). The rapid spread of rifampin-resistant *S. pneumoniae* strains within hospitals and communities may limit the role of rifampin combination therapy in meningitis.

(iii) Summary. The data supporting rifampin combination therapy for the treatment of *S. pneumoniae* infections is limited to animal models and case reports. However, with the difficulty in performing clinical meningitis studies, the Infectious Diseases Society of America meningitis guidelines suggest considering adding rifampin to vancomycin and ceftriaxone if there are concerns for a cephalosporin-resistant *S. pneumoniae* isolate and only if the isolate is known to be susceptible to rifampin (247).

***Legionella*.** Rifampin combination therapy with a macrolide or a quinolone for the treatment of *Legionella* pneumonia has been used for over 20 years. The addition of rifampin to a macrolide, in particular erythromycin, was used prior to the newer respiratory quinolones as salvage therapy for the treatment of *Legionella* pneumonia (108). The use of combined quinolone-rifampin chemotherapy for *L. pneumophila* has decreased with the expanded respiratory system activity of the broad-spectrum quinolones.

(i) *In vitro* and *in vivo* data. Both rifampin and the quinolones have activity against *Legionella* sp., *in vitro* and *in vivo* models of experimental pneumonia have found ciprofloxacin to be as effective as rifampin, and the combination did not improve responses or reduce the emergence of resistant mutants (114, 171). Further studies with newer quinolones have shown them to be equally effective as monotherapy as with rifampin combination therapy (18, 72, 106, 252).

(ii) Clinical data. Most of the clinical data were obtained from case reports of successfully salvaging patients failing erythromycin monotherapy for *Legionella* pneumonia (24, 81). Many patients were immunocompromised or infected with *Legionella micdadei* (24, 81, 240). The respiratory quinolones have made the macrolide-rifampin combination redundant. This is of great importance for organ transplantation, where the combined drug interactions of erythromycin and rifampin may make it complicated to manage the immunosuppressive levels of drugs such as cyclosporine and tacrolimus (4, 24, 49).

(iii) Summary. With the newer respiratory quinolones being very active against *Legionella* strains, there are insufficient clinical data to support the addition of rifampin to a quinolone or macrolide for the treatment of legionellosis (18, 72, 106, 252).

***Rhodococcus*.** *Rhodococcus equi* is an organism that causes fatal pneumonia in foals but can also cause cavitary pneumonia in immunocompromised humans. The organism lives within macrophages, similar to tuberculosis, and can be seen intracellularly on biopsy specimens of lesions (228) Therefore, the infection is difficult to treat and requires antibiotics that obtain high intracellular concentrations. Rifampin in combination with vancomycin, a macrolide, and/or a quinolone is used for the treatment of this infection (60, 164, 173, 244). Clinical

failure with rifampin resistance isolates has been reported and occurred with less than 2 drug combinations or in the absence of surgery for large lesions (11, 188).

Resistant Gram-negative organisms. The emergence of multidrug-resistant Gram-negative bacteria, in particular *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, and the lack of new classes of antimicrobials to treat them have led physicians to utilize rifampin as combination therapy (9, 34, 193).

(i) *In vitro* and *in vivo* data. An *in vitro* study assessed 33 isolates of *P. aeruginosa* against a combination of ticarcillin and tobramycin with rifampin. The combination of antimicrobials had a synergistic effect, with a fractional inhibitory concentration (FIC) of <1, including 8 of 16 isolates that were resistant to timentin and/or tobramycin. However, when either timentin or tobramycin was combined without rifampin, the MIC for resistant isolates exceeded obtainable serum concentrations for 12 of 13 resistant isolates (282). Kumar et al. demonstrated that the three-drug therapy of *Burkholderia cepacia* infection consisting of ciprofloxacin, imipenem, and rifampin had a greater clinical effect than any two-drug combinations (150).

There are also *in vitro* studies evaluating the combination of rifampin and imipenem, azithromycin, ampicillin-sulbactam, and colistin against multidrug-resistant (MDR) *A. baumannii* strains (102, 156, 242, 259). The use of these multiantibiotic combinations with rifampin has not led to observed rifampin resistance that had previously been described (45, 89, 269). The combinations appeared to be effective regardless of whether the organism was carbapenemase resistant or colistin resistant (156, 242, 259). These *in vitro* studies are limited, but they provide useful information such that investigators could develop antibiotic comparison studies with and without rifampin.

(ii) Clinical data. The first clinical report of three-drug therapy (a carboxypenicillin, an aminoglycoside, and rifampin) was of 4 patients with MDR *P. aeruginosa* endocarditis, ventriculoperitoneal shunt infection, and neutropenia. Despite two deaths, no rifampin-resistant strains emerged (272). More recent case series used rifampin combined with colistin and imipenem for the treatment of MDR *P. aeruginosa* osteomyelitis diabetic foot infections over 6 weeks (225, 226). Two of the 8 patients had treatment failures due to colistin toxicity (239). Saballs et al. prospectively evaluated the addition of rifampin to imipenem for the treatment of 10 seriously ill patients with carbapenem-resistant *A. baumannii* infections. Four of the patients had ventilator-associated pneumonia (VAP), one had bacteremia, and five had surgical-site infections. There were three deaths, while five of the seven survivors developed high-level rifampin resistance and required other procedures to resolve their infection (215). This should have been an expected result, as in that study, they were effectively using rifampin monotherapy, which would lead to rifampin resistance.

Two larger studies evaluated rifampin-colistin combination therapy for MDR *A. baumannii* infections in intensive care unit (ICU) settings. The first was an observational study evaluating rifampin (10 mg/kg b.i.d.)-colistin combination therapy for 26 patients (176). The cases treated with combination therapy had a mixture of bacteremia and pneumonia but had a low severity of illness (APACHE II score of 6). Outcomes were favorable, except for hepatic dysfunction for three patients, likely due to rifampin (176). Bassetti et al. also performed a prospective case series using rifampin-colistin for MDR *A. baumannii* infections of 29 patients in an ICU (22). Their study had data for 10 patients with bacteremia and 19 with pneumonia and had a greater severity of illness (APACHE II score 17) than the first report. Those authors reported 6 deaths but no hepatotoxicity, nephrotoxicity, or rifampin resistance (22). Both of these studies were limited by the absence of a control group for comparison of colistin monotherapy (22, 176).

(iii) Summary. The collective data for rifampin combined with colistin are limited to several small studies without controls, and therefore, this treatment cannot be recommended. Any future clinical study would be difficult to evaluate because patients with these MDR infections frequently have a greater severity of illness, and obtaining any beneficial results would be surprising (193).

Antifungal Therapy

The role of combination therapy of rifampin with amphotericin B for treating fungal diseases is of historical interest only and will not be endorsed in any way. The rationale for using this combination 30 years ago was to diminish the toxicity of conventional amphotericin B, as there were no other treatment options (126). The early *in vitro* data for treatment with rifampin and amphotericin B showed killing, despite the lack of laboratory testing standards, of *Histoplasma*, *Candida* species, *Cryptococcus*, *Rhizopus* sp., and *Aspergillus* sp. (27, 50, 75, 95, 126, 148, 172). The combination had no effect on a *Coccidioides immitis* murine model (126). There are two case reports of amphotericin B-rifampin therapy successfully treating a leukemic patient with pulmonary aspergillosis and another patient with endocarditis caused by *Wangiella dermatitidis* (212, 255). It is recommended that rifampin be avoided with new azoles such as voriconazole because it markedly decreases drug levels (71, 99, 182).

CONCLUSION

There is a minimal amount of compelling data to support rifampin combination antimicrobial therapy for the treatment of nonmycobacterial infections. There is a lack of significantly controlled clinical studies, and it is doubtful that any large randomized clinical trials will be performed in the future to assess rifampin combination therapy. Therefore, its use is reliant upon noncomparable *in vitro* or *in vivo* data or retrospective case reviews with their subsequent limitations and biases. There has been no standard practice used to define the appropriate rifampin dose required, when to initiate the rifampin with another antibiotic, and for how long a patient should remain on therapy. The most prominent observation from this review is that rifampin combination therapy appears to have improved treatment outcomes when there is a low organism burden for infections such as those with biofilms (i.e., PJI and PVE) but in general does not offer any benefits over antibiotic monotherapy for high-organism-burden infections such as NVE. Also, the failure to obtain source control through surgical debridement or removal of the focus of infection results in frequent treatment failures and the emergence of rifampin-resistant strains.

This review shows that rifampin combination therapy may be

clinically effective for the treatment of biofilm infections, especially for the salvage of PJI due to MSSA after debridement, and with vancomycin for the treatment of CoNS prosthetic heart valve infections. However, the combination of rifampin and vancomycin has not demonstrated any benefit over vancomycin monotherapy against MRSA (including hVISA) infections in either laboratory or clinical studies. When this combination is used, an emergence of rifampin-resistant mutants while on therapy frequently occurs. Rifampin combination therapy with either daptomycin, fusidic acid, or linezolid for the treatment of MRSA infections appears promising, with less emergence of resistance, but there are very few supporting clinical data at present. Rifampin combination therapy may be clinically beneficial for patients with penicillin-resistant pneumococcal meningitis, ventriculitis, and *Rhodococcus* infections. However, the role of rifampin combination therapy for the treatment of MDR Gram-negative organisms needs further evaluation and cannot be recommended.

Lastly, before considering adding rifampin to another antimicrobial agent, consider the risks of the toxicity of the drug, the associated drug interactions, and, importantly, whether the benefit, if any, is likely to outweigh the risk over using one effective antibiotic.

ACKNOWLEDGMENT

We thank Peter Choe for assistance with formatting the tables.

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